DOSAGE FORMS: NON-PARENTERAL

Shailesh K. Singh
Wyeth–Ayerst Research, Pearl River, New York, U.S.A.

Venkatesh Naini
Barr Laboratories, Inc., Pomona, New York, U.S.A.

INTRODUCTION

Dosage form is a drug delivery system designed to deliver the active ingredient to the body and, upon administration should deliver the drug at a rate and amount that assures the desired pharmacological effect. Such dosage forms are manufactured under current good manufacturing procedures (cGMP), using equipment and packaging to ensure product stability. The dosage form must produce the same therapeutic response each time it is administered. To maintain this reproducibility between and within batches, manufacturing procedures are validated under a specific quality assurance program. Non-parenteral dosage forms can be categorized based on the route of administration or physical form. Based on physical form they can be classified as solids, liquids (homogenous and heterogeneous systems), semisolids, and aerosols. Dosage forms can also be categorized based on the route of administration. Solid dosage forms include different types of compressed tablets, granules, troches, lozenges, coated dosage forms, and hard and soft gelatin capsules. Liquid dosage forms include solutions, suspensions, emulsions, and buccal and sublingual sprays. Topical dosage forms are applied to the skin and include ointments, pastes, creams, lotions, liniments, and transdermal patches. Some dosage forms are formulated for application to body cavities, viz. rectal and urethral suppositories and vaginal pessaries. Inhalation aerosols, using metered dose inhalers (MDIs), dry powder inhalers (DPIs) and nebulizers, are used to deliver drugs to the respiratory tract. Nasal route uses solution and suspension dosage forms. Occular route is used to administer solutions and suspensions to the eye for local and systemic effects.

SOLID DOSAGE FORMS

Powders and Granules

Powders are intimate mixtures of dry, finely divided drugs and/or chemicals that are intended for oral administration or external use. Powders may also be formulated as larger particle sized, free-flowing granules to aid in handling and administration. Bulk powders usually are packed into a suitable wide-mouth container and contain relatively nontoxic medicaments in large doses, e.g., compounded magnesium trisilicate oral powder. Insufflations are medicated powders blown into ear, nose, or throat.

Tablets

Flowability and compressibility are two important parameters essential for successful manufacture of tablets. Flowability determines ease of material flow from tablet hopper to the press. Inadequate flow gives rise to arching, bridging, or rat-holing in hoppers. Powder flow can be improved mechanically by use of force feeders. Flowability can also be increased by incorporation of glidants like fumed silica and talc. Another method involves the conversion of powder to spherical particles by spray drying or spheronization. Tablets are manufactured by dry and wet methods. Dry methods consist of direct compression, slugging, and roller compaction of drug-excipient blends. Directly compressible excipients may be disintegrants with poor flow, e.g., microcrystalline cellulose (Avicel PH102); free-flowing materials which do not disintegrate, e.g., dibasic calcium phosphate (DiPac®); or free-flowing powders which disintegrate by dissolution (e.g., spray-dried lactose, anhydrous lactose, dextrose, sucrose, amylose, etc.). The drug is mixed with excipients in a blender and then compressed directly on a tablet press. Dry granulation by compression or slugging is used for moisture or heat sensitive actives. The powder blends are compressed into compacts or slugs. An alternative method is to squeeze the powder blends into solid cake between rollers called roller compacts. These slugs or compacts are milled and screened in order to produce granules with improved flow. Granulation is the process of particle size enlargement of homogeneously mixed powder ingredients and simultaneously increasing bulk density, flowability, and compressibility of the system. Wet granulation process involves the massing of the powder mix, using a binder and

Table 1 List of commonly used tablet diluent/fillers

Diluent	Properties
Dextrose	Hygroscopic and soft granules; available as anhydrous and monohydrate; anhydrous has poor compression
Dicalcium phosphate	Inexpensive, insoluble in water; commercially Ditab® is unmilled while Encompress® is of specific particle size (better flow)
Alpha lactose monohydrate	Inexpensive, relatively inert; most widely used; often used with Avicel® PH MCC to improve disintegration
Mannitol	Freely soluble, used particularly for chewable tablet; powder form has poor flow and compaction; granular form has good flow
Microcrystalline cellulose	Excellent compressibility, some disintegration properties; available in different grades with specific applications
Sodium chloride	Freely soluble, used for solution tablets
Sucrose	Sweet taste but hygroscopic, may be diluted with lactose

solvent. The solvent should be volatile, nontoxic, and removed by drying. This process is not suitable for hydrolysable and thermolabile drugs. The binder is added in the form of a solution, or added dry or its mucilage incorporated with the powder blend. The choice of liquid depends on the properties of the material being granulated. Water is widely used alone or along with a binding agent. Commonly used nonaqueous liquids are isopropanol and ethanol. Massing process is usually performed in a low or high shear granulator where the liquid is poured or sprayed onto a moving powder bed until a moist mass of finely divided material is formed. This is passed through an oscillating granulator with the appropriate screen size to obtain the required granule particle size. Sometimes both intra- and extra-granular portions are divided to prevent incompatibility between excipient material hiding or better distribution, tableting or dissolution. Tablets require different functional excipients for their manufacture. Diluents are inert bulking agents added to actives to make a reasonably sized tablet. Generally, a tablet should weigh about 50–60 mg and therefore very low dose drugs will require these diluents to make at least a 50 mg tablet. Table 1 lists some commonly used excipients. Adsorbents such as fumed silica and kaolin are sometimes used for holding large amounts of fluids in an apparently dry state. Binders are used as adhesives to bind powder in wet granulation and give strength to compacts during compression. Binders may be incorporated into the dry blend or added as a solution to the mixed powder during wet granulation. Table 2 lists some of the binders commonly used in tableting. Disintegrants are usually added to promote rapid breakup of tablets to increase surface area and aid drug dissolution. Disintegrants can act by different mechanisms such as like swelling and capillary action. Table 3 lists some commonly used disintegrants. Glidants are materials that are added to tablet formulations to improve flow properties of the granulation. They act by reducing inter-particulate friction (e.g., fumed silica). Lubricants are added to prevent the adherence of granules to the punch and die faces of the tablet press. Many lubricants also facilitate flow of granules. Talc and magnesium stearate are more effective as punch lubricants. Stearic acid works better as a die lubricant. Table 4 lists some commonly used lubricants and glidants.

Specific Types of Tablets

Lozenges: These are compressed tablets formulated, without a disintegrant and must be allowed to dissolve in the mouth. They are used for local activity (throat lozenges) or for systemic effect (vitamins).

Effervescent tablets: These tablets undergo quick dissolution of actives in water due to internal liberation of carbon dioxide. By combining alkali metal carbonates or bicarbonates with tartaric or citric acid, carbon dioxide is liberated when placed in water. They are prepared by the heat fusion technique. Usually a water-soluble lubricant is used to prevent scum formation at the water surface. Sweetness is achieved by the addition of saccharin, since sucrose is hygroscopic and increases the bulk of the tablet, e.g., Rochelle Salt®.

Chewable tablets: These tablets are preferred for pediatric and geriatric patients who have difficulty swallowing whole tablets. Another advantage is that they do not need water for administration. Mannitol is normally used as the base diluent because of its pleasant taste and texture, and because it can effectively mask the taste of objectionable actives. They are usually prepared by wet granulation and are not compressed very hard. High amounts of flavor are added to increase

Table 2 List of commonly used binders in tableting

Binders	Concentration (wt%)	Properties
Natural gums (acacia, tragacanth)	1–5	Form very hard granules; variability in quality
Cellulose derivatives	2–5	HPMC is the most common; used as wet binders
Gelatin (replaced by synthetic polymers)	5–10	Strong adhesive, hence used in lozenges; gels when cold; not very popular in tropical climates
Glucose	Up to 50	Strong adhesive; but hygroscopic
Polyvinyl pyrrolidone (PVP)	2–20	Soluble in water and some organic solvents; (may vary with molecular weight grades)
Starch mucilage	5–10	Commonly used adhesive; insoluble in dry state
Pre-gelatinized starch	10–25	A better alternative to starch paste
Sodium alginate	0.5–3	Forms hard granules; prolongs disintegration time
Sucrose NF	Up to 70	Hygroscopic; tablet hardens on storage

palatability. Antacids are typically formulated as chewable tablets.

Sublingual and buccal tablets: These tablets are placed under the tongue (sublingual) or the cheek (buccal) and can produce immediate systemic effects by enabling the drug to be directly absorbed through the mucosa by preventing the first pass effect (e.g., isoprenaline sulphate and glyceryl trinitrate). Tablets are small, flat, without a disintegrant, and are compressed lightly to produce soft tablets.

Molded tablets: These are prepared from mixtures of medicinal substances and a diluent usually consisting of lactose and powdered sucrose in varying quantities. The powders are dampened with solutions containing high proportions of alcohol depending on the solubility of the active and filler. The dampened powders are pressed under low pressure in die cavities. Solidification depends upon crystal bridging during the subsequent drying process, and not upon the compaction forces.

Multi-layered tablets: A multilayered tablet consists of several different granulations compressed on top of each other to form a single tablet. They may also be bi-layer when incompatible drug substances are used, e.g., phenylephedrine HCl in one layer and ascorbic acid and paracetamol in another.

Modified Release Dosage Forms

Modified release (MR) has been used to describe dosage forms having drug release characteristics based on time, course, and/or location and are designed to accomplish therapeutic or convenience objectives not offered by conventional or immediate release dosage forms. Drugs for chronic conditions with short half-lives, possessing a good therapeutic index and uniform absorption pattern are ideal candidates for such dosage forms. These are either delayed release or extended release (ER) preparations. ER dosage

Table 3 List of commonly used tablet disintegrants

Disintegrants	Concentration (wt%)	Commercial name; property
Alginic acid and alginates	2–10	
Carbondioxide		Created in situ in effervescent tablets
Ion exchange resins		Amberlite®
Magnesium aluminium silicate	Up to 10	Veegum®; often slightly colored
Microcrystalline cellulose	Up to 20	Avicel; lubricant properties; directly compressible
Starch NF	5–20	Starch 1500® (pre-gelatinized starch)
Sodium dodecyl sulphate	0.5–5	Primarily a wetting agent but this aids disintegration
Sodium carboxymethyl cellulose	1–2	Nymcel®
Sodium starch glycolate	2–8 (dry)	Primojel®; Explotab®
Starch	5–10	Corn, potato, maize are most frequently used
Croscarmellose sodium	2–4	Ac-Di-Sol®; It may be used both at inter- and intra-granular portions (1–2%)
Cross linked PVP	2–5	Polyplasdone XL®, Crospovidone NF

Table 4 List of commonly used lubricants and glidants in tableting

Excipient	Type	Concentration (wt%)	Property
Calcium and magnesium stearate	Lubricant	0.25–2	Reduces tablet strength, prolongs disintegration, insoluble in water, excellent lubricant
Stearic acid	Lubricant	1–4	More preferred as a die wall lubricant
Polyethylene glycol	Lubricant	2–5	M.W. 4000–6000, soluble in water, moderately effective
Liquid paraffin	Lubricant	Up to 5	Dispersion problems
Sodium lauryl sulphate (SLS)	Lubricant	0.5–5	Moderate lubricant with wetting properties, used with stearates
Sodium stearyl fumarate	Lubricant	0.5–2	Less sensitive to overblending and compressibility
Magnesium lauryl sulphate	Lubricant	1–2	Water soluble
Talc	Lubricant	1–2	Insoluble but not hydrophobic
	Glidant	0.2–0.3	
Colloidal silica (Aerosil®, Cabosil®)	Glidant	0.1–0.2	Excellent glidant
Starch	Glidant	0.2–0.3	Primarily disintegrant
Microcrystalline cellulose	Glidant	0.2–0.5	Primarily used as diluents/filler

forms allow at least a twofold reduction in dosing frequency as compared to the conventional dosage form. Delayed release dosage forms are designed to release all or a portion of drug at times much later than the time of administration. The delay may be time based or environment specific, as in enteric-coated dosage forms. Some other MR dosage forms include repeat action and targeted release dosage forms. Most controlled release products are good examples of ER dosage forms. These dosage forms can be classified by their mechanism of release and/or type of formulation. Coated beads, granules microspheres, and other particulate systems are pellet type controlled release dosage forms, where the drug is usually coated onto nonpareil beads (low dose) or made from granules composed of the drug (high dose). These pellets are further coated with functional coating agents (Eudragits®, HPMCs, Surelease®, etc.) to provide various release characteristics. These pellets can be used to fill capsules (e.g., Ornade Spansules®) or compressed at low pressure into tablets (e.g., Theo-Dur®). In some cases small mini-tablets of about 3–4 mm diameter can be compressed. These tablets function like pellets and can be used to fill capsules. Microencapsulation is a process of encapsulating microscopic drug particles with a thin wall of coating material. Several coating materials have been used including gelatin, ethylcellulose, and polyvinyl alcohol, e.g., Micro-K-Extencaps® (Wyeth–Ayerst Research). Matrix systems are dosage forms where drug substance is combined with hydrophilic cellulose polymers (excipient material), which slowly erode in the presence of body fluids. On hydration, the polymers behave like a gel and prevent the fast disintegration of the tablet. Diffusion from the gel controls the drug release (e.g., Oramorph SR® tablets). A multi-layered tablet consists of several different granulations compressed on top of each other to form a single tablet composed of two or more layers. Each layer is fed from a separate feed frame with individual weight control. Precompression tamping helps in good binding of layers. Also, reduced pressures prevent intermixing of granules during compression. They may be bilayer where IR/ER combination are used or mainly when incompatible drug substances is used. Sometimes the release from individual layers is controlled to give a drug delivery system, such as, Geomatrix® system (1). In some cases if the bulk density of the tablet is less than one, it floats in the gastric fluids thus extending the residence time in the gastrointestinal tract (GIT). Such dosage forms are called Hydrodynamically Balanced Systems (HBS), an example being Valrelease® (Roche). In some cases the drug is embedded inside inert polymeric matrices with materials such as polyethylene, polyvinyl acetate, and polymethacrylates. The granulations are then compressed into tablets. These inert matrices are excreted in the feces unchanged (e.g., Ferro-Gradumet® (Abbott). Some drugs form complexes resulting in slower dissolution and behave as extended release dosage forms, e.g., Rynatan® (Carter-Wallace). A slowly eroding tablet may be granulated with hydrophobic excipients (waxy lipophilic material) so that the drug leaches out over an extended period with an outer shell containing the IR dose (buffered aspirin). In some

cases a cationic or anionic drug solution can react with an insoluble resin to form a complex. This complex can be tableted, encapsulated or suspended in a vehicle, e.g., Tussionex Pennkinetic® Extended Release Suspension (Medeva). Osmotic pump drug delivery systems consist of a core tablet coated with a semi-permeable membrane with a fine orifice made by laser beams. The core usually forms two layers containing the active and osmotic agents. In the gastric fluids water is imbibed by the osmotic agent (pull) and then exerts pressure on the drug (push) in solution, out through the orifice. Such dosage forms are independent of pH of the gastric fluids and are termed as gastrointestinal therapeutic systems (GITS), e.g., Procardia XL® (Pfizer). Repeat action tablets consist of slow release inner core and a immediate release (IR) as in Repetabs® (Schering) or as bilayer IR/ER tablets. Delayed release dosage forms are used for drugs that are destroyed in the gastric fluids, or cause gastric irritation, or are absorbed preferentially in the intestine. Such dosage forms are enterically coated using materials such as cellulose acetate pthalate, shellac, and waxes. The coating allows the drug to release at higher pH (pH dependent) or by enzyme catalyzed reactions, e.g., Erythromycin or Aspirin delayed release dosage forms. Several forms of oral controlled release systems are available in the market; however, most of them are dependent on the rate at which the system passes along the gastro-intestinal tract. This can be overcome by regulating the release of the drug by physical chemical means, or by a process related to the environment in which the delivery system is present at the specific time (2).

Capsules

The word "capsule" is derived from the Latin word *capsula* meaning a small box. Gelatin, a substance of natural origin with unique properties, is the major component of capsules. Gelatin is used because it is nontoxic and readily soluble in biological fluids at body temperature. It has good film forming properties and, as a in water and water–gylcerol systems, undergoes reversible phase change from a solution to gel at only a few degrees above ambient temperature. There are two forms of gelatin (A and B) based on the method of manufacture from animal bone and skin. The properties important for capsule shell manufacture are viscosity and bloom strength. Hard gelatin capsules are firm and rigid while soft gelatin capsules are soft and flexible. This is because soft capsules contain a larger proportion of plasticizers like glycerol, sorbitol, propylene glycol, acacia, and sucrose. Varying proportions of plasticizers are added depending on the intended use of soft gelatin capsules. The colorants used consist of soluble and insoluble dyes. Titanium dioxide and iron oxide pigments are common, although recently aluminum lakes are being used. Preservatives are added to capsules to prevent microbial contamination. Moisture levels are also maintained at low levels to prevent bacterial growth on storage.

Hard gelatin capsules (HGCs)

Hard gelatin capsules are available in sizes ranging from size 000, (the largest) to size 5 (the smallest). The fill weight of capsule and tapped bulk density of the powder blend determines the selection of capsule size. Recently, better techniques for capsule sealing, like, self-locking and have made it possible for a range of materials. The filler material should not react with gelatin. Aldehydes lead to gelatin cross-linking affecting the integrity of the shell and water in the formula can act as a plasticizer. On the other hand, hygroscopic agents can make the capsule shell brittle. Powders filled into hard gelatin capsules should have good flow properties to maintain uniform fill weights during filling operations. Granules and pellets of spherical shape making them free-flowing and nonfriable are good candidates for capsule filling using gravitational systems or specialized dosing chambers to maintain uniform fill weight. In some instances, minitablets (filmcoated, nonfriable) can be filled into capsules to produce specialized dosage forms or to separate incompatible ingredients. A recent innovation in hard gelatin capsule filling is a revival of the old practice of filling liquids or semisolids. The main problem encounted is product leakage. This difficulty was overcome by using self-locking capsules and formulation techniques. The use of mixtures of material which are either thermosoftening or thixotropic in nature has become prevalent. These materials are liquefied by heat or shearing force, and revert to solid state within the capsule shell after filling. Filling machines have been developed to handle such formulations with existing powder filling equipment. This system works with solid, liquid, semisolids, and potent drugs. The application of semisolids filling is also getting prevalent. A more recent innovation in HGCs to fill liquid dosage forms with the use of new machines which heat-seal the caps permanently to prevent leakage as observed with liquid filled HGCs in the past. A good example is the introduction of Licaps® (Capsugel) for liquid fills. Capsules made of nongelatin ingredients for materials not compatible with gelatin are also available, e.g., cellulose (Vegecaps®).

Soft gelatin capsules (SGCs)

SGCs or softgels are continuous gelatin shells surrounding a liquid or semi-solid fill. These capsules are formed, filled, and sealed, all in one operation. These capsules are

available in different shapes and sizes. SGCs are preferred for drugs with poor compressibility, poor powder flow, mixing problem, unstable or poor solubility in gastric pH, and bioavailability problems. Such drugs can be solubilized or dispersed in a liquid, where dosage uniformity is more accurate. Some drugs that are liquid or that melt during compression are good candidates, if other means of tabletting are expensive. Gelatin used in SGCs has lower bloom strength than HGCs. The plasticizer type and concentration controls the mechanical strength of the shell. In general, plasticizer amounts are larger, making them more flexible than HGC shells. Preservatives, colorants, and opacifiers are used in the same manner as in HGCs. Sometimes softgel capsules are enteric coated for drugs which are absorbed in the small intestine. Once the capsule shells dissolve in vivo, the drug is available in a liquid or semi-solid form that dissolves or disperses into fine particles with enhanced bioavailability. SGCs can be filled with several materials such as aqueous solutions, nonaqueous solutions, suspensions, pastes, oily solutions of drug, self-emulsifying system, and water-miscible liquids. Materials that cause migration of water or plasticizer from the shell cannot be filled. Surfactants and systems with extreme pH should be avoided.

LIQUID DOSAGE FORMS

Solution

A solution is a homogenous single-phase system consisting of two or more components. Solutions are easier to swallow and are acceptable dosage forms for pediatric and geriatric use. The drug in solution is readily available for absorption and therapeutic response is faster. Solutions, however, are bulky and inconvenient to transport. The stability of actives is poorer than in solids and they provide suitable media for microbial growth. Aqueous solutions are preparations made with water as solvent. Purified Water USP is widely used for most preparations. Some drugs are unstable in water or sensitive to the presence of carbon dioxide or oxygen. Not all substances are completely soluble in water and may lead to precipitation. Several other techniques are used to increase solubility of drugs in solution. Cosolvency is a process of increasing solubility of a drug by using a combination of solvents. Some suitable cosolvents are ethanol, isopropyl alcohol, sorbitol, glycerol, and propylene glycol. If a drug is a weak acid or base, then its solubility in water is influenced by pH. The pH for optimum solubility may not give a stable product. Thus, a compromise must be reached to ensure proper formulation and bioavailability. Suitable buffer systems may be used if necessary. Solubility of insoluble or poorly soluble drugs can also be increased by addition of surface-active agents. Most surfactants are miscible with solvent system and compatible with other ingredients. Hydrophilic surfactants with HLB values >15 are generally preferred. In some cases complexation of a drug with a material may result in formation of soluble molecular complex. However, such complexation needs to be reversible for the active to cross the biological barrier. Chemical modifications of the drug can also result in more water-soluble derivatives. However, these modified drugs are regarded as new chemical entities. Nonaqueous solutions are used when complete solution is not possible in water or if the drug is unstable. Ethyl alcohol is the most widely used water-miscible solvent for external preparations. Ethyl ether is occasionally used as a co-solvent, in combination with alcohol in the preparation of some colloidons. Other solvents such as isopropyl myristate and isopropyl palmitate are solvents with low viscosity and are ideally used in cosmetics preparations. Xylene is present in ear drops for human use to dissolve ear wax.

Liquid formulation additives used include buffers, colorants, flavoring agents, and preservatives. Buffers are dissolved in solvents to resist pH changes. The choice of buffers depends on the pH and the buffering capacity. Most pharmaceutically acceptable buffer systems include carbonates, phosphates, citrates, gluconates, and lactates. Colors are added for attractiveness and product identification. Flavors are added to solutions to increase their palatability, particularly for drugs with unpleasant taste. This is especially useful in pediatric formulations. Flavors also help in product identification and are of natural or synthetic sources. Fruit juices, peppermint oil, and menthol are some examples of flavors. Some flavors are preferred for specific products, e.g., mint is associated with antacid formulas. Similarly, flavors are preferred by specific patient groups, e.g., children prefer fruity tastes and smell, while adults prefer flowery and acid flavors. Preservatives help prevent microbial growth. The choice of preservatives should be based on their performance from a microbial challenge test. Care should be taken to ensure there is no adsorption of preservatives onto product containers or packaging material. Antioxidants are added to prevent degradation of the drug in solution; the amount and type can be determined after careful determination of the degradation pathway and stability testing with different agents. Sucrose is widely used as sweetening agent, because it is water soluble, and stable at a wide range of pH. It has a pleasant texture and soothing effect on the throat. There are several other sweeteners that are less widely used. Artificial sweeteners like sugar alcohols and aspartame are used by diabetic patients.

Types of Liquid Preparations

Draught and elixirs: Draught is a mixture by which one or two large doses of about 50 ml are given. Traditionally, elixirs are solutions of potent or nauseating drugs containing alcohol as a cosolvent (60–70%).

Linctuses: A linctus is a viscous preparation usually prescribed for relief of cough. They usually consist of a simple solution of active in a high concentration of sucrose, often with other sweetening agents.

Mouthwashes and gargles: These are aqueous solutions for prevention and treatment of mouth and throat infections. They usually contain antiseptics, analgesics, and/or astringents. These solutions are used directly or diluted with warm water.

Nasal drops: These are small volume aqueous solutions. They are usually buffered to pH of 6.8 and are isotonic solutions. These drops are used locally as antibiotics, anti-inflammators, and decongestants.

Ear drops: These are simple solutions of drugs in water, glycerol, and propylene glycol for local use in the ear and include antibiotics, antiseptics, cleaning solutions, and wax softeners (xylene).

Enemas: These are available as solutions (aqueous or oily) as well as suspensions for rectal administration of drugs for cleaning, diagnostic, or therapeutic effect.

Lotions: These are available as solutions and suspensions to be applied topically without friction. They may either contain humectant, so that moisture is retained on the skin after application, or alcohol, which evaporates quickly imparting a cooling sensation to the skin.

Liniments: These are intended for massaging the skin. They may contain ingredients such as methyl salicylate or camphor as counter-irritants.

Colloidons: These are prepared from volatile solvents that evaporate quickly leaving a tough, flexible film on the skin that seals small cuts and or holds the active in intimate contact with the skin.

Intermediate solutions: Pharmaceutical solutions are used as intermediates for manufacturing other preparations. Aromatic water is used as a flavoring agent and peppermint and anise waters have some carminative properties. These are manufactured as concentrated waters and are diluted before use. Infusions are prepared by extracting the drug using 25% alcohol without heat. Extracts are similar to infusions, but are concentrated by evaporation. Tinctures are alcoholic or hydro-alcoholic solutions prepared from vegetable materials or from chemical substances. They are relatively weak compared to extracts. Spirits are alcoholic or hydro-alcoholic solutions of volatile substances prepared by simple solution or by admixture of ingredients. These are used as flavoring agents and may have medicinal value. Syrups are concentrated solutions of sucrose or other sugars to which medicaments or flavoring agents are added. These are bacteriostatic by virtue of their osmotic effect, e.g., simple syrup, USP.

Suspensions

These are liquids consisting of insoluble solid particles dispersed throughout a liquid phase. Most suspensions are ready to use while some are prepared as solids to be reconstituted just before use. Ideally, suspension should be homogenous between the time of shaking and dispensing the required dose. The suspended particles should be small, uniformly sized to give a smooth elegant product free from grittiness. Some insoluble solids are not easily wetted by water and thus need wetting agents to be able to disperse readily throughout the medium. Some wetting agents include surfactants, hydrophilic colloids, and solvents. Surface active agents or surfactants possessing HLB value between 7 and 9 are suitable as wetting agents. Most surfactants are used at concentrations of 0.1%. For oral use Tweens and Spans are commonly used, while sodium lauryl sulphate (SLS) is used for external applications. Some wetting agents may cause foaming and formation of deflocculated systems. Hydrophilic colloids like acacia, bentonite, tragacanth, alginates, and cellulose derivatives function as a protective colloid by coating the surface of the particles and thus imparting hydrophilic character to the solid particles. Solvents such as alcohol, glycerol, and glycols are water-miscible and reduce the liquid/air interfacial tension, increasing wetting.

Flocculation and deflocculation

Flocculation comes from the Latin word *flocculate* meaning loose and woolly. Flocculated systems result in rapid rate of settling because each individual unit is composed of many particles and is therefore larger. However, due to the loose packing of flocs they are easily dispersible on shaking. Deflocculated systems on the other hand are made up of smaller particles whose settling rate is slower, but the settled particles tend to form an irreversible compact and are difficult to redisperse. This phenomenon is called *caking*. For coarse suspensions, a deflocculated suspension will have better uniformity of dose but poorer stability due to formation of cake. Thus, a stable suspension is obtained by preparing a partially flocculated suspension with controlled viscosity so that settling is minimal. Controlled flocculation is achieved by a combination of particle size control, electrolytes to control zeta-potential and by the addition of polymers. Inorganic electrolytes, added to an

aqueous suspension alter the zeta-potential of the dispersed particle. Lowering the zeta-potential sufficiently will result in flocculation. Some of the commonly used electrolytes include sodium salts of acetates, phosphates, and citrates. Use of ionic surfactants may also result in flocculation by neutralization of particle charges. Starch, alginates, tragacanth, and cellulose derivatives are sometimes added to control the degree of flocculation so that the suspension is in a flocculated state and the sedimentation volume is large. Suspensions should exhibit high viscosity at low shear rate and vice versa. Also, the viscosity should be low enough to be poured from the container but should spread evenly, if it is intended for external application. Suspensions for injection should be able to pass through hypodermic needles. Acacia gum is used as a thickening agent for extemporaneously prepared suspensions. Tragacanth forms viscous aqueous solutions, and its thixotropic and pseudoplastic properties make it a better thickening agent than acacia. Sodium alginate is used as a suspending agent but is incompatible with cationic materials. Several cellulose derivatives, such as methylcellulose (Celacol®), hydroxyethylcellulose (Natrasol® 250), sodium carboxymethylcellulose, and microcrystalline cellulose, disperse in water to produce viscous colloidal solutions and are suitable, as suspending agents. Montmorillonite clays or hydratyed silicates like bentonite, veegum, and hectorite readily hydrate and absorb upto 12 times their weight of water. The gels formed are thixotropic and therefore have wonderful suspending properties. Carbopols® are synthetic polyacrylic acid copolymers that function as thickening agents at higher pH values.

Buffers are included in suspensions to maintain chemical stability and control tonicity. Density modifiers like sucrose and propylene glycol can be added to prevent large differences in densities that could result in sedimentation. Flavors, colors, and perfumes may be added to improve palatability and appearance of the product. Humectants like glycerol and propylene glycol are added in concentrations of 5% for external applications to prevent the product from drying out after application to the skin. Addition of preservatives is important, particularly when using naturally occuring adjuvants. In some situations sweeteners may be added but their affect on final product viscosity and degree of flocculation should be well understood. Suspensions are normally manufactured using colloidal mills with rotor–stator mechanism to ensure free flowing and evenly dispersed particles. Oral suspensions usually have flavoring agents intended for oral administration. Good examples are milk of magnesia, bentonite, magma, and jellies. All these systems swell and form a gel like consistency with non-Newtonian characteristics. Topical suspensions like Calamine lotion are for external use only.

Emulsions

These are dispersions of one liquid (dispersed phase) in the form of uniformly divided droplets in another liquid (dispersion medium). Depending on which liquid is the dispersed phase oil-in-water (o/w) or water-in-oil (w/o) systems are obtained. To test the identity, emulsion miscibility, staining and conductivity tests are performed. The choice of emulsion depends on the route of administration and the end use. For oral administration, o/w emulsions are used while for external use, both o/w and w/o systems can be employed. Semisolid o/w emulsions are termed as "creams," and are easily washable after application. Water-in-oil emulsions have an occlusive effect and are therefore preferred as moisturizing lotions and cleansing agents. The choice of oil depends on the application with some oils like castor and cod liver oil having a therapeutic value. Thus, w/o preparations are greasy, with high apparent viscosity while o/w emulsions are less greasy and readily absorbed and washable. Ideally emulsions should exhibit pseudoplasticity and thixotropy, that is, high viscosity at low shear rates and vice versa. They should be dispensable from containers, bottles, and tubes but at the same time should spread on the skin with light pressure. The rheological properties of emulsions are controlled by the concentration, particle size, and viscosity of dispersed phase, concentration of dispersion phase, and the nature and concentration of the emulsifier. The choice of emulsifying system depends on the route of administration, its HLB value and its toxicity. There is no approved list of emulsifiers but pharmaceutical companies employ emulsifiers approved for use in the food industry. Emulsifiers with surface activity reduce the interfacial tension between the phases, thereby decreasing the need for energy to disperse the internal phase. The surfactants used can be anionic like sodium, potassium, and ammonium salts of long chain fatty acids (e.g., sodium stearate), soaps of di- and tri-valents metal ions (e.g., calcium oleate and amine soaps, sulphated and sulphonated compounds (e.g., SLS). Cationic surfactant, amphoteric surfactants like lecithin, and non-ionic surfactants, like glycol and glycerol esters (e.g., glycerol monostearate), sorbitan esters, polysorbates, fatty alcohol polyglycol ethers (e.g., cetyl or cetostearyl alcohol), fatty acid polyglycol esters are also used. Sometimes naturally occurring materials and their derivatives, such as acacia, semi-synthetic polysaccharides (e.g., methylcellulose), sterol containing substances (e.g., beeswax), and wool fat

(anhydrous lanolin), can also be employed as emulsifiers. Other ingredients used in emulsions are finely divided solids, antioxidants, such as butylated hydroxy toulene (BHT) and butylated hydroxyanisole (BHA), humectants and preservatives like benzoic acid, parahydroxybenzoic acid esters, chlorocresol, and phenoxyethanol. Emulsions can be used orally (o/w) with the therapeutic agent included in the internal phase (as for taste masking bad tasting medicaments). Externally, they can be used as lotions either with therapeutic agents or without (as in cosmetics). Emulsions are made using a variety of equipment depending on the stability requirement and the kind of process used. Both batch and continuous processes can be used. Colloid mills have been used traditionally. However, high-pressure homogenizers, microfluidizers, and ultrasonic homogenizers are being used for manufacturing emulsions.

SEMISOLID DOSAGE FORMS

Ointments, creams, and pastes are semisolid dosage forms intended for topical application. They may be applied to the skin, used nasally, rectally, and vaginally. Most of them contain some form of medicament. Medicated ointments are semi-solid preparations intended for application to skin or mucous membranes. Nonmedicated ointments are used as protectants, lubricants, and emollients. Ointment bases used for ointment preparation are of four types, hydrocarbon bases, absorption bases, water-removable bases, and water-soluble bases. Hydrocarbon bases have emollient properties and are effective as occlusive dressings (e.g., Petrolatum, USP). Absorption bases permit the incorporation of aqueous solutions to form w/o emulsions (e.g., hydrophilic petrolatum and lanolin). Water-removable bases are also o/w emulsions and are water washable (e.g., hydrophilic ointment). Water-soluble bases have no oleaginous component and are referred to as *greaseless* water-washable bases (e.g., polyethylene glycol ointment). The potential for absorption depends on the choice of the bases, and intended use of the medicament. Appropriate selection of ointment bases is important for dermal therapy. Ointments for rectal preparation (e.g., Tronolane® ointment for hemorrhoidal analgesia) and vaginal preparations (e.g., Mycelex-7® ointment as antifungal) are available in the market. Creams are semisolid emulsions with one or more medicinal agents intended for external use. The so called *vanishing creams* are o/w emulsions with stearic acid and cold creams are w/o emulsions with an oily base. Creams spread more easily than ointments and are preferred by some patients. Gels are semisolid systems with dispersions of small or large molecules in an aqueous vehicle with a gelling agent e.g., high molecular weight Carbopols® that are cross-linked polyacrylic acid. Some gels like milk of magnesia or magma has two phases. These behave as thixotropic systems with the viscosity changing due to a *gel–sol* transition on shaking. Pastes are ointments with large amount of powder levigated into the base and are intended for application to the skin. Pastes are more hygroscopic than ointments and are used to absorb serous secretions. (e.g., zinc oxide paste). Plasters are solid or semisolid masses spread on backing paper, plastic, or fabric. Nonmedicated forms are termed as *adhesive plasters* while medicated plasters provide a therapeutic effect at the site of application. Some medicated plasters are termed as *cataplasm*, e.g., ibuprofen (3) and salicylic acid plasters. Transdermal drug delivery systems (TDDS) are used for delivery of actives through the skin into the systemic circulation. Several methods have been used to facilitate the transport of active through the barriers of the skin. Certain absorption enhancers are used to temporarily increase permeability of the skin for increased delivery. More recently, iontophoretic techniques have allowed the delivery of charged chemicals across the skin using an applied electric field (e.g., amino acids and proteins). Sonophoresis or high-frequency ultrasound is also being studied as a means of effectively enhancing transdermal delivery of drugs. Transdermal delivery systems are of two main types the monolithic matrix system that contains the excess drug dispersed in the polymeric matrix and cast into a matrix with a backing layer and frontal membrane, e.g., Estraderm® (Novartis). Membrane-controlled transdermal patches contain drug reservoir in the form of a gel or saturated solution of drug with a backing adhesive and a rate controlling membrane e.g., Transderm-Scop® (Novartis). Currently, the market is flooded with a variety of transdermal systems for smoke cessation and hormonal delivery patches. More recently efforts are on to develop transmucosal delivery patches.

OTHERS DOSAGE FORMS

Suppositories are solid dosage forms intended for insertion in body cavities like rectum, vagina, and occasionally in the urethra for local or systemic effects. The length, shape, and weight of these depend on the body cavity it is used for. These melt, soften, or dissolve after application depending on the type of suppository base applied. Cocoa butter base suppositories usually melt in contact with the

body temperature. Other bases, such as polyethylene glycol, glycerin, and soap based suppositories solubilize. Cocoa butter suppositories are hydrophobic, and dissolve oil soluble drugs but absorption is poor in the aqueous rectal fluids. Thus, better absorption is obtained with water-soluble bases. Rectal suppositories can be used for local (hemorrhoids) or systemic effects. Systemic bioavailability is poor and the amount of drug required is more than oral administration. Vaginal and urethral suppositories are usually used for their local effects (e.g., anti-infectives). Rectal suppositories weigh about 2 g and have varying shapes like bullets and torpedoes. Urethral suppositories are thin pencil-shaped with tapered ends. Vaginal suppositories are globularized and weigh about 4–5 g. Generally absorption from suppository bases rectally is better when the rectum is empty. Particle size of solids plays an important role in absorption. Most importantly rectal absorption allows to bypass the first pass effect. Most suppositories are manufactured by molding from melts or by compression.

AEROSOL DOSAGE FORMS

Aerosols are pressurized dosage forms containing one or more active drug dissolved, suspended, or emulsified in a propellant or a mixture of solvent and propellant, which is released on actuation of the valve as a fine dispersion of liquid or solid in a gaseous medium. Aerosols are intended for topical administration; for administration into body cavities; for administration orally or nasally as fine solid particles or liquid mists through the pulmonary airways, nasal passages, or oral cavity (buccal or sublinual). Those that provide an airborne mist are called space sprays; those intended for carrying actives to surface are termed as surface sprays and other are termed foam aerosols. Aerosol consists of product concentrate and the liquefied propellant. The pressure depends on the types and amounts of propellants and the nature and amount of active present. Propellant is a liquefied gas or mixture of liquefied gas, which serves as the solvent, or vehicle. In some cases nonliquefied gases like nitrogen, and carbon dioxide are used. Space aerosols (85% propellant) operate at 30–40 psig at 70°F. Surface aerosols (30–70% propellant) operate between 22–55 psig at 70°F. Foam aerosols operate at a slightly higher pressure. Foam aerosols are emulsions of the propellant and product concentrate. Aerosols can be two-phase systems comprising of a solution of drug in liquefied propellant and a vapor phase of propellant/gas. Some of them are present as three-phase systems, comprising of water-immiscible propellant, an aqueous product concentrate or drug in suspension/emulsion and a vapor phase. Aerosol containers are made from glass (coated and uncoated), tin, aluminum, and stainless steel containers. There are various forms of spray valves and metered valves (for more accurate dosing of potent drug). Oral aerosols are mostly used via the buccal route, e.g., Nitrolingual® spray that emits nitroglycerin at a dose of 0.4 mg per metered dose. The respiratory tract offers several advantages for administration of drugs. Inhalation systems should be capable of producing fine particles, usually <10 μm for effective drug delivery. Inhalation drug delivery has been traditionally used to treat respiratory disease, but in recent times the lung has been used as a portal for administering drugs to the systemic circulation. With their large effective surface area, the lungs offer an attractive route for systemic drugs. Three main dosage forms, viz. metered dose inhalers (MDIs), dry powder inhalers (DPIs), and nebulizers have gained prominence (4). Metered dose inhalers are pressurized systems consisting of drug suspension in a propellant and may contain other additives such as surfactants, antioxidants, and solvents, although some solution systems are available. Traditionally MDIs have been formulated using chloroflurocarbons (CFCs). These propellants are now being phased out under the terms of the "Montreal Protocol" due to their ozone depleting potential (5). This has resulted in an increasing urgency to reformulate existing MDI formulations with alternative hydroflurocarbon (HFC) propellants such as HFC-143a and HFC-227. Formulations using the new propellants have recently won FDA approval (Airomir®, 3M Pharamceuticals). To offer better coordination between actuation and patient inhalation of the emitted dose, several spacer devices are available (Nebuhaler®, AeroChamber®, and Breathancer®) with marketed MDI formulation. Recent trends in devices include the breath actuated MDI (Autohaler®, 3M Pharmaceuticals), where the patient inhalation triggers the dose. Due to the phase out of CFCs and extensive difficulties in reformulating using HFCs, dry powder inhalers, and nebulizers are becoming popular. Dry powder inhalers consist of mixtures of micronized drug and a large particle size carrier (usually lactose). These drug-carrier ordered mixtures are packaged in unit doses (capsules or blisters), as in Spinhaler® (Fisons Pharmaceuticals) and Rotahaler® (GlaxoWellcome Pharmaceuticals) or as pure drug bulk powder, which can be metered into single doses (Turbohaler®, AstraZeneca Pharmaceuticals). In many instances the patients inhalation maneuver causes the active particles to separate from the carrier in the air stream. More recently, to overcome intra-patient variability in dosing, active DPIs have been designed (Dryhaler®, Dura Pharmaceuticals). In these devices, the patient's breath triggers a deaggregation mechanism, which

separates the drug particles from the carrier, which are then inhaled. Newer fine particle generation technologies, such as spray drying and supercritical fluid extraction, are being used to produce fine particles of drug including proteins and peptides for delivery to the deep lung. This can facilitate the use of inhalation delivery systems for systemic drug delivery. Nebulizers generate fine mists from aqueous and nonaqueous drug solutions, using either compressed air or ultra-sonication. Their main disadvantage is that they are bulky and are not portable. Recent developments in this field have focused on the development of battery operated portable devices, which can nebulize aqueous solution containing minimal, or no preservatives.

PEDIATRIC AND GERIATRIC DOSAGE FORMS

Physiology plays an important role in the development and performance of different functions in the body. It is important to determine their consequence on dosage form development. Pediatric dosing is usually determined by weight and age. FDA classifies the pediatric groups into neonates, infant, child, and adolescent. There are several excipients that have been reported to cause adverse reactions, e.g., azo dyes cause bronchoconstriction, lactose may cause prolonged diarrhea and intolerance, and sweeteners such as saccharin are weak carcinogens. Alcohol is a common solvent for most pediatric OTC liquid products. However, limits on the alcohol content of OTC products have been set to minimize toxicity in children. Oral administration is the preferred route for children. However, children younger than 5 years have difficulty swallowing solid tablets. Thus, oral liquid is the most preferred dosage form in pediatric patients. Liquids are often unstable and have short expiration and accurate dosing is difficult. Recently, there has been increased interest in chewable tablets and "sprinkle" powders in capsule formulations as they are well received by children with dentition. Rectal administration is not popular because of wide variability in absorption. Pulmonary administration is emerging to be a popular delivery mode for children, but needs to be studied further for systemic effects. Transdermal route may be another area to explore for children, since the stratum corneum is well developed in children as in adults. This may be beneficial as an alternate route for children. Pediatric drug therapy has very few drug delivery systems. There has been some in-roads made with OTC cough and cold products. However, most industries do not have resources to perform separate studies for safety and efficacy in children (smaller consumer than adults) for new chemical entities. Perhaps FDA should take initiatives to provide pharmaceutical companies with returns like tax break or patent extension and specific market for such developmental work especially for life threatening diseases (6).

Apart from alterations in the pharmacodynamics (PD) and pharmacokinetics (PK), the geriatric population suffers from a number of chronic conditions and physical limitations. Clinical monitoring becomes very important to titer dosing accurately. Most of their PK and PD processes take a down turn. Absorption is slower from the oral cavity. In general, the aged skin is more permeable to water and other chemicals. However, the clearance to the blood stream is lowered thus distribution may not be complete. Physically, impairment or decline in vision may hinder one's ability for self-medication. Also, swallowing and chewing may be a problem in elderly patients. For example, patients suffering from dry mouth may have difficulty swallowing a tablet or capsule. Similarly, elderly patients who are edentulous (i.e., toothless) are incapable of chewing any tablet dosage form. Although sublingual and buccal tablets are used by the elderly population there is very less emphasis on its effect on bioavailability with aging. Patients with dry mouth condition may feel local irritation with such dosage forms. Capsules like tablets may hinder swallowing and are not advisable for elderly patients. Liquids are easier to swallow, but are usually not packaged as unit dosages. Patients with impaired vision and dexterity may not be able to accurately self-administer the required dose. The transdermal route seems to offer better compliance with elderly patients but bioavailability needs to be determined before using this route. Several alternative dosage forms and packaging techniques are emerging to improve compliance of dosage form in elderly patients. Several types of packaging aids like dosett tray, calender-packs and med packs are used to remind the dosing schedule for elderly patients. Granules of drug may be easy to swallow. They can be mixed with water or food and swallowed easily. Unit dose packs may still be difficult to use for some elderly patients. Effervescent tablets provide an alternative dosage form. These tablets dissolve in water to form a ready-to-use product. The use of an irregular shaped tablet that prevents it from lying flat may be another form that can help patients with impaired dexterity (e.g., Tiltabs®). Similar to granules the drug may also be presented in the form of a small amount of concentrated solution for the entire dose, e.g., 5 ml Rapamune® concentrated oral solution (Wyeth–Ayerst Research). Such products can be mixed with food or drink. This is similar to the use of a dispersible tablet that forms a uniform stable suspension when dispersed in water. Emerging technology has focussed on newer dosage forms like the use of quick or rapid dissolving technology (RDTs), wherein, the dosage form quickly dissolves in the mouth and rapid absorption of

the drug can occur systemically or even from the mouth (7). Furthermore, compliance in elderly patients has also resulted in the availability of sugar and sodium-free products that are beneficial for such age groups.

NEW DRUG-DELIVERY TECHNOLOGIES

Newer technologies are emerging as we move into the new millenium. These technologies promise to have lots of benefits such as simplifying administration regimens, enhancing compliance, improving clinical benefits, and reducing overall healthcare costs. Rapid-dissolving tablets (RDTs) are designed for patients who have difficulty in swallowing standard tablets/capsules, such as pediatric and geriatric patients. These include the lyophilized foam from Zydis® (Claritin Reditabs), Flashtab® (Prographarm), Orasolv® (Cima Labs), Wowtabs® (Shaklee), and Flashdose® (Fuisz Technology) (8, 9). Hydrogel based technology offered by Professor Neil Graham of British Technology group for development of several systems including morphine suppositories. Nanocrystal™ technology offered by Elan Corporation where the crystalline drug (<400 nm) is thinly coated with a surface modifier to impart physical stability. Liquitard® is a liquid taste masking sustained release granules as a suspension and is offered by Eurand America (10). Inhale Therapeutics offers proprietary technology for pulmonary delivery of proteins and peptides, using innovations in powder processing to develop formulations for deep lung delivery for systemic and local indications (10). Jago Pharma developed the Geomatrix® systems which involves the use of multilayered hydrophilic matrix systems (10). Several newer excipients are now available as matrices for controlled delivery. These include polysaccharides from Galactomannan such as guargum and locust bean gum (e.g., $Timer_x$ Technology (11). Considerable research efforts have been towards the development of safe and efficient chitosan-based dosage forms (12). The development of solid-lipid nanoparticles (SLN) have made it possible for delivering drugs with less side-effects, better targeting, and protection from enzymes (13). Zambon group in Europe has developed Timeclock® technology that involves coating solid drug with hrdrophobic surfactant. Chronotropic drug delivery, which targets delivery to a specific absorption window for local as well as systemic effect. Emisphere® technology uses a carrier that binds to drug molecules noncovalently to form a complex (14). These complexes easily cross the membranes and then dissociate to release the active. Theratech uses the Theriform® microprinting technology to develop oral and implantable dosage form for making Microdose® tablets (15). Delsys Corporation has revolutionized their Accudep® technology of electrostatic deposition of dry powder to any surface with great accuracy (16, 17). Labopharm Inc. has developed Contramid® technology obtained by cross-linking of high-amylose starch in three dimensional network which is combined with the active. Once in the stomach, the tablet surface turns into a gel and the active diffuses at an even rate. PORT™ (Programmable Oral Release Technology) is a technology platform to resolve drugs with biopharmaceutical problems. PORT™ is a capsule based system with opportunity to provide multiple prolonged release of one or more drugs. This technology is applicable to a wide variety of drug classes and can be used to achieve difficult PK profiles, e.g., zero order with burst system. Quadrant Healthcare has engineered micron-sized particles with enhanced stability and PK profiles (10). Solidose® technology is based on chemically modifying oiligosaccharides to make them more hydrophobic. In contact with body fluids they undergo phase change and release the drug. Several self-emulsifying and lipid-based systems have been developed that form micro-emulsions of water-insoluble drugs for oral delivery (18). DanBiosystems has developed a proprietary Targit® technology, which involves enteric coating with azo polymers, which degrade only at specific sites by bacterial enzymes. Ethypharm is another company involved with coating of nano- and micro-particles, using supercritical fluid (CO_2) technology, suited for fragile water-soluble molecules (peptides and proteins) (10, 19). Protarga™ is another company which is involved in the development of dosage form by covalently attaching fatty acids (docosahexaenoic acid or DHA) to actives to create new compounds that can be taken up by cells targeted for treatment. A lot of focus has been directed to tissue engineering that is used to design biological substitutes or regenerate natural tissues for defective or lost tissues and organs through the use of cells and their scaffolds (20, 21). Fentanyl Oralet® (Abbott labs) is a lollipop that has painkillers used as preoperative sedative. Several forms of intra-vaginal drug delivery systems like Progestasert® system (Alza Corp.) and Dinoprostone® vaginal insert have been developed. Implants like the levonorgestrel Norplant® device (Wyeth–Ayerst Research) that is incorporated as contraceptive on the upper arm. Similarly, Gliadel® wafers (Guilford Pharmaceuticals) are implanted in the brain tumor cells.

CONCLUSION

Non-parenteral dosage forms can be administered by different mechanisms. In recent years there has been a

plethora of emerging drug delivery technology companies. Most of these technologies are addressing issues related to unique delivery systems and selectivity of these systems for affected organs or diseases. However, rarely it recognized that improvements in drug therapy are a consequence of not only the new chemical entity but also the combination of active and the delivery system (dosage form). Currently the trend is to develop a delivery system and then look for suitable drug candidates to apply. This needs to be changed to gain understanding of what unmet medical need is the active aimed for, the rate, time and site for the active to be delivered and then provide a suitable delivery system. More emphasis should be made on the improvement of drug effect profile. Thus, the future of drug delivery will depend on how they can contribute to drug therapy for unmet medical needs (22).

REFERENCES

1. Conte, U.; Maggie, L.; Colombo, P.; LaManna, A. Multi-Layered Hydrophilic Matrices as Constant Release Devices (Geomatrix^{TM} Systems). J. Controlled Release **1993**, *26*, 39–47.
2. Swarbrick, J. Advances in Controlled Drug Delivery. S.T.P. Pharm. Pratiques **1996**, *6* (1), 53–60.
3. Agarwal, V.; Singh, S.K.; Reddy, I.K.; Durranu, M.J.; Khan, M.A. Cataplasm–Based Controlled Drug Delivery: Development and Optimization of a Novel Formulation. Drug Dev. Ind. Pharm. **1999**, *25* (5), 659–665.
4. Gonda, I. The Ascent of Pulmonary Drug Delivery. J. Pharm. Sci. **2000**, *89* (7), 940–945.
5. McDonald, K.J.; Martin, G.P. Transition to CFC—Free Metered Dose Inhalers—Into the New Millennium. Int. J. Pharm. **2000**, *201* (5), 89–107.
6. Nahata, M.C. Lack of Pediatric Drug Formulations. Pediatrics **1999**, *104* (3), 607–609.
7. Sastry, S.V.; Nyshadham, J.R.; Fix, J.A. Recent Technological Advances in Oral Drug Delivery—A Review. Pharm. Sci. Tech. Today **2000**, *3* (4), 138–145.
8. Habib, W.; Khankari, R.; Hontz, J. Fast –Dissolve Drug Delivery Systems. Crit. Rev. Ther. Drug Carrier Sys. **2000**, *17* (1), 61–72.
9. Chang, R.; Guo, X.; Burnside, B.A.; Couch, R.A. Fast-Dissolving Tablets. Pharm. Technol. **2000**, June, *52–58.*
10. Evers, P. *Developments in Drug Delivery: Technology & Markets*; Healthcare and Pharmaceutical Publishing: London, 1995; Financial Times.
11. Altaf, S.; Yu, K.; Parasrampuria, J.; Friend, D.R. Guar Gum–Based Sustained Release Diltiazem. Pharm. Res. **1998**, *15* (8), 1196–1201.
12. Illum, L. Chitosan and Its Use as a Pharmaceutical Excipient. Pharm. Res. **1998**, *15* (9), 1326–1331.
13. Pinto, J.F.; Muller, R.H. Pellets as Carriers of Solid Lipid Nanoparticles (SLN) for Oral Administration of Drugs. Pharmazie **1999**, *54* (7), 506–509.
14. Leone-Bay, A.; Leipold, H.; Agarwal, R.; Rivera, T.; Baughman, R.A. The Evolution of an Oral Heparin Dosing Solution. Drugs Future **1997**, *22* (8), 885–891.
15. Kastra, W.E.; Palazzolo, R.D.; Rowe, C.W.; Giritliglu, B.; Teung, P.; Cima, M.J. Oral Dosage Forms Fabricated by Three–Dimensional Printing. J. Controlled Release **2000**, *66*, 11–17.
16. Chrai, S.S. Electrostatic Dry Deposition Technology. Pharm. Tech. **1998**, *4*, 106–112.
17. Houston, S. A Revelution in Dose Form Manufacture. Manuf. Chemist. **1998**, *6*, 20–21.
18. Charman, W.N. Lipids, Lipophilic Drugs, and Oral Drug Delivery—Some Emerging Concepts. J. Pharm. Sci. **2000**, *89* (8), 967–978.
19. York, P. Strategy for Particle Design Using Supercritical Fluid Technologies. Pharm. Sci. Tech. Today **1999**, *2* (11), 430–440.
20. Langer, R. Selected Advances in Drug Delivery and Tissue Engineering. J. Controlled Release **1999**, *62*, 7–11.
21. Tabata, Y. The Importance of Drug Delivery Systems in Tissue Engineering. Pharm. Sci. Technol. Today **2000**, *3* (3), 80–89.
22. Breimer, D.D. Future Challenges for Drug Delivery. J. Controlled Release **1999**, *62*, 3–6.

FURTHER READING

Ansel, H.C.; Allen, L.V.; Popovich, N.G. *Pharmaceutical Dosage Forms and Drug Delivery Systems*, 7th Ed. Lippincott's Williams and Wilkins: 1997.

Banker, G.S., Rhodes, C., Eds.; *Modern Pharmaceutics*, 3rd Ed.; Marcel Dekker, Inc.: New York, 1996.

Block, L.H.; Yu, A.B.C. Pharmaceutical Principles and Drug Dosage Forms. *Comprehensive Pharmacy Review*; Shargel, L., Mutnick, A.L., Souney, P.F., Swanson, L.N., Block, L.H., Eds.; Williams & Wilkins: 1997; 28–76.

Byron, P.R., Ed.; *Respiratory Drug Delivery,* CRC Press: Boca Raton, FL, 1990.

Chien, Y.W. *Novel Drug Delivery Systems*; Marcel Dekker, Inc.: New York, 1992.

General Information/Pharmaceutical Dosage Forms. *USPXXIV*; The United States Pharmacopoeial Convention, Inc. Rockville MD, 2000, 2107–2117, <1151>.

Hickey, A.J., Ed.; *Pharmaceutical Inhalation Aerosol Technology* Marcel Dekker, Inc.: New York, 1992.

Hickey, A.J., Ed.; *Inhalation Aerosols: Physical and Biological Basis for Therapy*; Marcel Dekker, Inc.: New York, 1996.

Lachman, L., Lieberman, H.A., Eds.; *Pharmaceutical Dosage Forms: Tablets*; Marcel Dekker, Inc.: New York, 1980–1982; 1–3.

Lachman, L., Lieberman, H.A., Kanig, J.L., Eds.; *Theory and Practice of Industrial Pharmacy*, 4th Ed., Lea & Febiger: Philadelphia, 1987.

Martin, A.N., Swarbrick, J., Cammarata, A., Eds. *Physical Pharmacy,* 3rd Ed., Lea & Febiger: Philadelphia, 1983.

Robinson, J.R.; Lee, V.H.L. *Sustained and Controlled Release Drug Delivery*, 5th Ed., Marcel Dekker, Inc.: New York, 1995.

Shargel, L.; Yu, A. *Applied Biopharmaceutics and Pharmacokinetics*; Appleton & Lange: 1999.